AD_____

Award Number: DAMD17-03-1-0204

TITLE: A Multidisciplinary Evaluation of Mild Traumatic Brain Injury: Early Predictors of Outcome

PRINCIPAL INVESTIGATOR: Patricia Dischinger, Ph.D.

CONTRACTING ORGANIZATION: University of Maryland, Baltimore
Baltimore, MD 21203

REPORT DATE: April 2006

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-04-2006	Annual	1 APR 2005 - 31 MAR 2006

4. TITLE AND SUBTITLE
A Multidisciplinary Evaluation of Mild Traumatic Brain Injury: Early Predictors of Outcome

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-03-1-0204

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Patricia Dischinger, Ph.D.

E-mail: pdischin@som.umaryland.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Maryland, Baltimore
Baltimore, MD 21203

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
Original contains color plates: All DTIC reproductions will be in black and white.

14. ABSTRACT

The purpose of this study is to identify a cohort of patients with mild Traumatic Brain Injury and follow them for 1 year post-injury to determine injury outcomes and identify factors that best predict long-term sequelae.
The third year has been dedicated to continued subject recruitment and follow-up. Human subjects approval was obtained from both the University and Army review boards.
Data entry and validation are an ongoing process which also includes data back-up and migration. Laboratory protocols continue for the collection, storage, and processing of blood samples for the S-100b tests. We have preliminary data on 108 samples. Preliminary data analysis has been initiated, as 43 of 80 one-year follow-up evaluations have been completed.
As of March 31, 2006, 147 subjects have been recruited. Since current recruitment to date has fallen short of the original target of 300 subjects, a request for a no-cost extension through March 31, 2007, was filed on January 31, 2006, and approved February 8, 2006, which would allow continued recruitment of subjects through September 30, 2006. Adjusted target enrollment of 190-200 subjects with follow-up evaluations will continue through December 31, 2006.

15. SUBJECT TERMS
Mild Traumatic Brain Injury (MTBI); injury; balance; s-100 Beta protein and neuron-specific enolase;

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
U	U	U	UU	20	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

INTRODUCTION

Each year approximately 1.5 million Americans sustain a traumatic brain injury (TBI). The most common causes of TBI are due to blunt force trauma. The goal of this research is to identify a cohort of patients with mild TBI and follow them for a period of one year (1) to determine injury outcomes and (2) to identify those factors that best predict those patients with long-term sequelae. Approximately 200 subjects will be identified over the life of the study. These subjects will have a baseline assessment during the initial trauma center admission, which includes biochemical markers, balance measures, clinical findings and neurometric tests. Follow-up testing will be completed at 3-5 days, 7-10 days, 3 months, 6 months and 12 months post injury.

BODY

Recruitment and Follow-up:

This is the annual report for year 3 of the study. The third year focused on subject recruitment and follow-up as well as preliminary data analysis. As of March 31, 2006, 147 subjects have been recruited. Since current recruitment to date has fallen short of the original target of 300 subjects, a request for a no-cost extension through March 31, 2007, was filed on January 31, 2006, and approved February 8, 2006. Included in the extension was an adjusted target enrollment of 190-200 subjects. We will be continuing with recruitment of subjects through September 30, 2006 and follow-up evaluations through December 31, 2006. Less than one-year follow-up will be completed for those subjects recruited after December 2006. We will obtain as much follow-up data as possible, continue with data analysis and provide a final report next year.

Actual screening and recruitment was initiated on October 6, 2003. As of March 31, 2006, 2,142 subjects were screened and 147 recruited. Table 1 describes the reasons and frequencies for the 1,995 subjects who were not recruited. Over one-third of the subjects were not recruited because they had associated injuries. This includes such things as brain injury requiring intervention, a spinal cord injury or thoracic injuries requiring intubations.

Table 1: Reasons potential subjects were not recruited	#
Age	**7**
Non-local resident	**34**
No LOC, MS changes	**221**
Mini Mental Status Score <8/10	**21**
Non-English speaker	**85**
Associated injuries (i.e., brain injury requiring intervention, thoracic injuries requiring intubation)	**679**
Discharged before enrollment completed	**258**
Refused	**170**
Penetrating injury	**7**
Other (i.e., past medical history, active military, probation/parole)	**508**
Readmits	**5**

The overall follow-up rate is depicted in Table 2. The follow-up ranges from a high of 85% at 7-10 days post-injury to a low of 52% at 12-months post-injury. We believe the return rate is so high at 7-10 days because many subjects return to the STC clinic for follow-up appointments at that time and we attempt to arrange our evaluations on the same day. The follow-up rate decreases throughout the remainder of the study. This may be due to the fact that many subjects have returned to normal activities and therefore are not available for follow-up.

Table 2: Follow-up Status of the 147 Enrolled Subjects*			
	Completed	**Eligible**	**Follow-up Rate**
Evaluation	**N**	**N**	**%**
3-5 day	**107**	**144**	**74**
7-10 day	**120**	**141**	**85**
3 month	**79**	**132**	**60**
6 month	**65**	**118**	**55**
12 month	**43**	**82**	**52**
*An evaluation is considered complete if we were able to complete the interview and the symptom checklist.			

The details of follow-up status are described in Table 3. Telephone follow-ups occur at a much higher rate during the acute phase of recovery as opposed to later on in recovery (31% at 3-5 days versus 5% at 12-months post-injury). Nine subjects have been withdrawn from the study (8 withdrew consent and 1, a neurosurgical intervention, was initiated after consent was obtained). It should be noted that percent completion rates are fluid as recruitment and follow-up are still ongoing.

Table 3: Detailed Description of Follow-up Status of the 147 Enrolled Subjects							
	Complete*	Partial**	Telephone	DNKA***/ Cancels	Withdrawn	Lost F/U****	Eligible
	N	N	N	N	N	N	N
Initial	14	133	na	na	0	0	147
3-5 day	9	52	46	36	1	0	144
7-10 day	27	45	48	18	3	0	141
3 month	28	29	22	46	3	4	132
6 month	38	10	17	39	9	5	118
12 month	31	7	5	25	9	5	82

*Complete=all evaluation components assessed
** Partial= one or more evaluation components not assessed
*** DNKA= did not keep appointment
**** F/U= follow-up

Human Subjects Protections / Protocol Modifications:

During year three, one modification (removing three support staff) was made to the study protocol or procedures. The University of Maryland, Baltimore (UMB), Human Research Projects Office (HRPO) Institutional Review Board (IRB) provided re-approval for the protocol for a one-year period beginning May 20, 2005.

This past year the entire research staff completed the Certified Investigator Training Initiative (CITI) as required by UMB HRPO.

New Personnel:

As described in last year's report, initially we had one post doctorate student who was on campus every day conducting the neuropsychological evaluations. In year two we expanded the neuropsychological staff to three post doctoral students who covered the neuropsychological evaluations, allowing for greater flexibility for conducting follow-up examinations. During year three, we had one person primarily responsible for the neuropsychological evaluations but found it necessary to have five persons trained to provide coverage on an as-needed basis. This has helped provide a more flexible schedule for subject follow-up visits.

Staffing / Training:

Since the beginning of the project the speech language pathology team has remained fairly constant. One staff member resigned her position at the University of Maryland Medical Center during the past year but expressed interest in remaining involved in the project. The current complement of four staff members allows for adequate coverage.

Safety:

Safety for subjects and evaluators is always a concern, and therefore we continue to monitor the environment to ensure the safety of our subjects and our staff.

Space Allocation:

The study space has remained constant throughout the past year and there are no anticipated changes.

Manual of Operations:

The Manual of Operations continues to be updated as necessary.

Team Meetings:

Meetings of the study team occur on a regular basis. We use this time to discuss issues related to recruitment, follow-up and patient recovery. Additional small group meetings are held as needed. These meetings focus on specifics such as data analysis for the various components of the study.

Data Entry and Storage:

As previously reported, one clinical coordinator and the part-time recruiter are responsible for all data entry and the second clinical coordinator is responsible for auditing the data. In addition, prior to analysis a secondary data validation is completed and changes to the data are recorded.

Data Analysis:

Preliminary data analysis has been initiated on all evaluation components now that follow-up evaluations through 12 months have been completed on 43 of 80 potential subjects who have met the one-year anniversary of their injury.

ANAM Proprietary Issues:

All study staff administering the ANAM (Automated Neuropsychological Assessment Metrics) or ARES (ANAM Readiness Evaluation System) are required to sign usage agreements, as the software is the proprietary information of the USAMRMC. Software usage as well as data collection, storage and analysis will be consistent with the user agreement.

S-100 beta testing:

The procedure to ensure timely retrieval and freezing of blood samples per testing guidelines and moving of the samples to the research lab for storage until ready for bulk processing continues. The guidelines for processing the blood samples to obtain S-100β values indicate that the blood samples be run in batches of thirty. Thus far we have received preliminary results for the first 108 subjects.

Recent literature indicates that S-100β may not be a specific marker for brain injury as it has been found to be increased in patients without brain injury.[1-4] Anderson reported the S-100β was highest in those with bone fractures, followed by thoracic contusions without fractures.[1] In addition several studies have indicated that S-100β has not been a significant predictor of symptoms associated with TBI nor neurocognitive performance following TBI.[2-4] Stalnacke and colleagues indicated that S-100β may be more useful in predicting disability and may be useful in identifying those patients with mild TBI that might benefit from rehabilitation services.[3]

Other biochemical markers for TBI have also been reported in the literature and they include two monomers (S100A1B and S100BB) that comprise the S100β and Glial Fibrillary Acid Protein (GFAP).[1;2;5-7] With respect to S100A1B and S100BB, Anderson et al, found both types of monomers in trauma patients without head injuries. The A1B and BB concentration ratio varied, indicating no correlation with the type of trauma or tissue damage. In a study by de Boussard et al, the mean values of S100AB were significantly higher in patients with mild TBI and in patients with mild orthopedic injuries when compared with non-injured controls. The authors also noted a significant correlation between time of injury to the first blood draw and concentrations of S100BB but not S100β and S100A1B. The investigators also noted that mean values of these biomarkers were higher in patients with radiological findings, but there was no relation between S100β, S100A1B, S100BB concentrations and symptoms. They concluded that the S100AIB seems to be more specific for brain injury than S100β in patients with milder TBIs. Recent reports indicate the GFAP, which is only found in glial cells of the central nervous system, may prove to be a better marker for TBI outcomes. The studies of GFAP involved only severe TBI but have shown that GFAP predicts outcome at 3-, 6-, and 12-months post trauma. In a study by Pelinka et al, it was demonstrated that GFAP was not increased in trauma patients without TBI nor was there a correlation between concentration levels and timing of samples. To our knowledge there have been no studies examining the predictive value of GFAP in mild TBI patients. In light of reported

discrepancies in the recent literature regarding the validity of the S-100 markers with respect to diagnosis and outcomes of mild TBI and the lack of research involving GFAP in mild TBI patients, we feel that further investigations are warranted. Our preliminary results indicate that persons with higher S-100β are reporting fewer symptoms than those with lower S-100β concentrations. We are continuing our analyses in order to explain this phenomenon. We are questioning whether this result is related to the fact that the multiply injured subjects may be more focused on symptoms associated with their orthopedic and systemic injuries and have not yet returned to situations (i.e., work/school) where post-concussive symptoms would be more noticed.

Neuropsychological testing:

All study staff administering the ANAM or ARES signed usage agreements, as the software is the proprietary information of the USAMRMC. Software usage as well as data collection, storage and analysis are consistent with the user agreement.

The ANAM, including the ARES and Word Memory Test (WMT) constitute the neuropsychological battery of tests that are designed to measure cognitive, emotional and motivational functioning. The ANAM is a battery of tests designed to measure simple and choice reaction time, divided attention of visual and spatial skills, running memory and executive reasoning. The WMT, a brief paper and pencil test, measures sensitivity to motivation and embellishment of cognitive deficits, i.e. 'malingering'.

Reaction time is emerging in the literature as a measure sensitive to the effects of concussion.[8] We have examined the relationship between S100β protein, measures of simple (sRT) and choice reaction (pRT) and a weighted composite of several other tests (wTP) at 7-10 days and 3-months post-injury. Results of analyses indicated a significant relationship between S100B protein levels and sRT at 7-10 days ($t=3.91$, $p=0.0004$) such that as S100B levels increased, sRT scores decreased. No other significant relationships were found. Although a relationship existed between S100B and sRT at 7-10 days, it disappeared by 3 months; this may be explained by literature suggesting that the effects of mild TBI resolve within the first several months of injury.

S100B protein levels have been linked to disability after mild TBI.[3] The Word Memory Test (WMT) is a test of effort and motivation that is viewed as more sensitive to levels of effort than to brain injury.[9] We assessed the relationship between S100B and effort, as measured by the WMT, in our sample of subjects with mild TBI. Subjects were evaluated at 7-10 days (N=46) and 3 months (N=41) post injury. As expected, results of analyses indicated no relationship between S100B protein levels and performance on the WMT (both immediate recall and delayed recall trials) at either time point. This provides evidence of the utility of the WMT when assessing mild TBI populations, where effort is often an issue.

The literature is mixed regarding the effects of depression and anxiety on neuropsychological performance in mild TBI samples.[10] Forty-six participants were

assessed with the ANAM at 3 months post injury. Results of regression analyses adjusted for age, gender, education, and S100B levels indicated no difference between 1) depression, 2) anxiety, or 3) depression or anxiety on sRT, pRT, or wTP. These findings suggest no group differences regarding depression and/or anxiety mood states on measures of simple reaction time, choice reaction time, or overall neuropsychological functioning. Although depression and anxiety may be common in mild head injury, it did not mediate deficits observed on measures of neuropsychological functioning in this sample.

Although these results are preliminary, we will replicate them when the study is complete as well as include similar analysis for 6- and 12- month follow-up visits.

We have discussed what battery of neuropsychological tests would be useful in future studies and we have determined that we would continue with the ARES and ANAM. However we have decided that replacing the paper and pencil version of the WMT would be more appropriate since the rest of the battery is computerized. Also, we agreed it would be useful to add a neuropsychological component to the telephone follow-ups. This would consist of a structured interview that would assess areas related to neuropsychological functioning such as memory, concentration, and coping with day to day activities.

Cognitive testing:

Speech and Language Pathologists (SLP) from the University of Maryland Medical Center have been responsible for conducting cognitive evaluations on study subjects using the SCATBI (Scales of Cognitive Ability for Traumatic Brain Injury). Based on meetings with the SLP[11] and a review of literature there have been no recent reports using the SCATBI in mild TBI population. Currently, the SCATBI can take up to 45 minutes to administer and the SLP are interested in determining scientifically if there are components of the SCATBI that would be more useful in predicting long-term cognitive issues associated with mild TBI. In addition, the SLP have developed a brief instrument for assessing cognitive ability based on clinical experiences and are very interested in determining its predictive power in a population of mild TBI patients. In this study, we elected to administer the SCATBI at the 3-month follow-up evaluation to determine its usefulness in predicting outcomes beyond the current 7-10 clinical use. Our preliminary investigations of the SCATBI results indicate that higher levels of functioning, based on reasoning and recall continue to improve throughout the three months following injury. Based on this information and anecdotal information provided at the 6-month and 12-month follow-ups, in a future study we would like to continue using the SCATBI throughout the follow-up period.

Balance testing:

We continue to conduct two clinical balance tests on study subjects at each evaluation period. Since we have expanded the criteria to include subjects with associated injuries, we correctly anticipated the initial balance tests rates would be low. Initial balance tests are being completed on 11% of the enrolled subjects. The rate continues to improve with each subsequent visit when subjects return to the hospital for follow-up (3-5 day 22%; 7-10 day 41%; 3-month 60%; 6- and 12-month 82%). On the data we have analyzed thus far, we have noticed improvements in overall postural stability through the 7-10 day follow-up period with a leveling off at 3-months that continues to one year. We will be conducting analyses to determine if balance measures predict long-term outcomes associated with TBI.

Initial balance deficits have been noted among athletes sustaining a mild TBI. Balance tests results along with neuropsychological measures have been suggested as a means of determining ability to return to play among these injured athletes. Similar issues are faced by military personnel in determining return to duty among injured soldiers. In a study by Guskiewicz et al, they concluded that more research is needed to determine the best neuropsychological battery for assessing sport-related concussion. Since most of the studies assessing balance focus on sport-related injuries we feel it is necessary to investigate balance related issues as they related to mild TBI sustained by other mechanisms of injury. This information would hopefully be beneficial to the military in determining return to duty status among mild TBI victims.

Other assessments:

We continue to monitor symptoms at each follow-up session whether in person or by phone. Fatigue, headache and dizziness were the most frequently reported symptoms 3-5 days post-injury, all of which were above pre-injury reported levels. By one year post-injury the symptoms had decreased from peak levels but remained above pre-injury reported levels for headache and dizziness. Based on preliminary analysis the frequency of reporting four or more symptoms at 12-months post-injury (29%) was similar to pre-injury (26%); however, the severity (based on frequency, duration and intensity) was greater. At the three month follow-up, the proportion of subjects with physical symptoms had returned to baseline levels, whereas emotional and cognitive symptoms remained elevated. Future analysis will focus on the frequency or severity of reported symptoms.

General well being is assessed at every time point except 3-5 days post-injury. Initial results reveal that positive well being is lowest at 7-10 days post-injury but continues to improve throughout the follow-up period. We have noticed that positive well being at 12 months exceeds baseline values in the subjects who have returned for this follow-up. We will continue with data analysis to focus on the specific domains of well being which include vitality, depression, anxiety, positive well being, general health, and self-control.

KEY RESEARCH ACCOMPLISHMENTS

Preliminary analyses thus far indicates:

- There was a significant relationship between S-100B and Simple Reaction Time at 7-10 day post-injury after controlling for age, gender and education.
- There was no relationship between S-100 B and Choice Reaction Time or the Neuropsychological Composite score at 7-10 days post-injury.
- There was no relationship between S-100 B and performance on WMT at 7-10 days and 3-months post-injury.
- Following injury, the number of symptoms reported increased dramatically; 26% reported ≥ 4 symptoms prior to injury; at 3-5 days this rate increased to 73%, declining to 39% by three months.
- Symptoms with highest prevalence at 3-5 days included fatigue (86%), headache (62%) and dizziness (54%).
- Three months post-injury emotional and cognitive symptoms remained elevated and physical symptoms returned to pre-injury levels.
- Predictors of symptomatology 3 months after injury include increasing age and female gender.
- Tests of simple reaction time at 7-10 days post-injury predicted symptoms and well being at 3 months.
- No positive association was noted between S-100 B and symptoms at 3 months. In fact, those with lower S-100 B levels reported more symptoms.

REPORTABLE OUTCOMES

Abstracts Submitted, Accepted and Presented:

Lee-Wilk, Terry, Dischinger, P.C., Mackenzie, C.F., Murdock, K.R., Imle, P.I., Spector, J., Kufera, J.A., Auman, K.M., Thysen, J., and Kane, R.L. The Relationship Between S100B Protein and Neuropsychological Performance in Mild Traumatic Brain Injury. Poster presentation at the annual meeting of the International Neuropsychological Society, Boston, MA, February, 2006.

Thysen, J., Lee-Wilk, T., Mackenzie, C., Kane, R.L., Spector, J., Auman, K.M., Kufera, J.A., Murdock, K.R., Imle, P.I., and Dischinger, P.C. The Relationship Between S100B Protein Levels and Effort in Mild Traumatic Brain Injury. Poster presentation at the annual meeting of the International Neuropsychological Society, Boston, MA, February, 2006.

Dischinger PC, Cooper C, Mackenzie, Romani W, Spector J: Serial Assessment of Mild Head Injury: Early Predictors of Outcome, Department of Defense Military Health Research Forum, San Juan Puerto Rico, April 25-28, 2004

The following abstracts were submitted and accepted for presentation after March 31, 2006.

Dischinger PC, Cooper CC, Kane RL, Mackenzie C, Romani W, Ryb GE and SAMHI Research Team: MILD TRAUMATIC BRAIN INJURY: PREDICTORS OF LONG-TERM OUTCOMES, Department of Defense Military Health Research Forum, San Juan Puerto Rico, May 2006

Lee-Wilk, T; Kane, RL.; Mackenzie, C; Spector, J; Murdock, KR; Kufera, JA; Auman, KM; Imle, PC; Thysen, J; Lonser, K; Dischinger, PC: THE EFFECTS OF DEPRESSION AND ANXIETY ON NEUROPSYCHOLOGICAL PERFORMANCE IN MILD TRAUMATIC BRAIN INJURY, American Psychiatric Association Annual Meeting, Toronto Canada, May 2006

Abstracts Submitted awaiting review:

Ryb GE, Dischinger PC, Murdock, KR; Kufera, JA; Auman, KM; Imle, PC; Thysen, J; Lonser, K; Dischinger, PC: PREDICTORS OF POST-CONCUSSIVE SYMPTOMS AT THREE MONTHS, submitted to American Association for the Surgery of Trauma (AAST).

CONCLUSIONS

We have completed year three of the study and have continued to gain great insight into the logistics involved in carrying out research within the mild TBI population. Recruiting subjects within the acute care trauma setting is often not easy, even with the relaxed criteria. Part of this difficulty may be attributable to the fact that the subjects, having been through a life changing event, are not open to the suggestion of participating in a study, and are ready to go home. As we stated last year, another issue may be related to the fact that many patients have other injuries, and may not be as concerned, at that point in time, about their mild head injury. We originally anticipated that subjects would not return for follow-up and therefore our follow-up rate would be very low. This however has not been the case. The return to hospital follow-up ranges from 51% at 7-10 days to 39% at 6-months post-injury.

As of March 31, 2006 we have enrolled 147 subjects. Preliminary data analysis has been initiated on all evaluation components and is ongoing.

A no-cost extension for this study was requested and approved on February 8, 2006, to allow recruitment through September 30, 2006 and to achieve a final target enrollment of 190-200 subjects, two-thirds of the original target.

We are in the process of developing a grant that expands on the work of the current study. We plan to include additional biochemical markers that have been shown to be related to TBI outcomes. In addition, we will be including heart rate variability measures that have been shown to be correlated with severity of injury.[12] To our knowledge, no study has documented the prognostic value of heart rate variation (pre-injury, on admission, at discharge and at follow-up) in relation to the development of post-concussive syndrome, neuro-cognitive and emotional disturbances among mild TBI victims. We also intend to include Magnetic Resonance Imaging (MRI) in our future research. Refinements in MRI (i.e., Diffuse Tensor Imaging(DTI)) has higher sensitivity in the diagnosis of Diffuse Axonal Injuries (DAI)[13] which are not seen on conventional imaging. Positive findings on conventional MRI have been shown to be correlated with slower reaction times but have an overall poor correlation with neuro-cognitive outcome.[14] We plan to investigate whether DTI-MRI is an adequate tool to identify mild TBI patients with significant cognitive deficits, as this has not been evaluated. We also plan to expand our follow-up questionnaires to include more questions on functional and lifestyle components that have been reported as important outcomes by current study subjects.

REFERENCES

1. Anderson RE, Hansson LO, Nilsson O, Dijlai-Merzoug R, Settergren G. High serum S100B levels for trauma patients without head injuries. *Neurosurgery*. 2001;48:1255-8discussion.

2. deBoussard C, Fredman P, Lundin A, Andersson K, Edman G, Borg J. S100 in mild traumatic brain injury. *Brain Inj*. 2004;18:671-683.

3. Stalnacke BM, Bjornstig U, Karlsson K, Sojka P. One-year follow-up of mild traumatic brain injury: post-concussion symptoms, disabilities and life satisfaction in relation to serum levels of S-100B and neurone-specific enolase in acute phase. *J Rehabil Med*. 2005;37:300-305.

4. Stapert S, de K, Houx P, Menheere P, Twijnstra A, Jolles J. S-100B concentration is not related to neurocognitive performance in the first month after mild traumatic brain injury. *Eur Neurol*. 2005;53:22-26.

5. Nylen K, Ost M, Csajbok LZ et al. Increased serum-GFAP in patients with severe traumatic brain injury is related to outcome. *J Neurol Sci*. 2005;240:85-91.

6. Pelinka LE, Kroepfl A, Leixnering M, Buchinger W, Raabe A, Redl H. GFAP versus S100B in serum after traumatic brain injury: relationship to brain damage and outcome. *J Neurotrauma*. 2004;21:1553-1561.

7. Vos PE, Lamers KJ, Hendriks JC et al. Glial and neuronal proteins in serum predict outcome after severe traumatic brain injury. *Neurology*. 2004;62:1303-1310.

8. Collins L, Long CJ. Visual reaction time and its relationship to neuropsychological test performance. *Archives of Clinical Neuropsychology*. 1996;11:613-623.

9. Green P, Rohling ML, Lees-Haley PR, Allen LM. Effort has a greater effect on test scores than severe brain injury in compensation claimants. *Brain Inj*. 2001;15:1045-1060.

10. Davidoff G, Roth E, Thomas P et al. Depression and neuropsychological test performance in acute spinal cord injury patients: lack of correlation. *Arch Clin Neuropsychol*. 1990;5:77-88.

11. Pike, B., Isbee, M, Atticks, A, and Roos, B. The Use of SCATBI Today. 2006. Ref Type: Personal Communication

12. Su CF, Kuo TB, Kuo JS, Lai HY, Chen HI. Sympathetic and parasympathetic activities evaluated by heart-rate variability in head injury of various severities. *Clin Neurophysiol*. 2005;116:1273-1279.

13. Hurley RA, McGowan JC, Arfanakis K, Taber KH. Traumatic axonal injury: novel insights into evolution and identification. *J Neuropsychiatry Clin Neurosci*. 2004;16:1-7.

14. Hoffman JM. New advances in brain tumor imaging. *Curr Opin Oncol*. 2001;13:148-153.

APPENDIX

ABSTRACT SUBMISSION
Annual meeting of the International Neuropsychological Society, Boston, MA, February, 2006.

The Relationship Between S100B Protein and Neuropsychological Performance in Mild Traumatic Brain Injury

Lee-Wilk, T., Dischinger, P., Mackenzie, C., Murdock, K., Imle, P., Spector, J., Kufera, J., Auman, K., Thysen, J.A., and Kane, R.L.

Objective: To assess the relationship between S100B protein (a biological serum marker of astroglial cell death representative of CNS damage) and measures of neuropsychological functioning in a sample of participants with mild traumatic brain injury (mTBI).

Participants and Methods: Thirty-four participants, ages 18-64, with mTBI (Glasgow Coma Scale 13-15) admitted to an emergency room of an urban hospital were included in this longitudinal study. S100B protein was measured by blood draw upon admission, within 3-10 hours post-injury. Participants were subsequently assessed (within 7-10 days of injury) with the Automated Neuropsychological Assessment Metrics (ANAM), a computerized library of tests designed to serially assess neuropsychological functioning. To reduce the number of variables, several test measures were combined into a weighted composite. In addition, we also included measures of simple (sRT) and choice (pRT) reaction time.

Results: Results of regression analyses adjusted for age, gender, and education indicated a significant relationship between S100 and sRT ($F=9.51$, $p=0.004$). There was no significant relationship between S100B and either the composite score ($F=0.49$, $p=0.488$) or pRT ($F=0.79$, $p=0.381$).

Conclusion: Our findings indicated a significant association between S100B protein and sRT. This finding is of interest since sRT is emerging in the literature as a sensitive measure to the effects of concussion. Findings from previous research have been mixed with studies finding and failing to find relations between S100B and performance on cognitive tests. In this analysis of data from our study, S100B was related to reaction time but not to more complex cognitive tasks.

APPENDIX

ABSTRACT SUBMISSION
Annual meeting of the International Neuropsychological Society, Boston, MA, February, 2006.

The Relationship Between S100B Protein Levels and Effort in Mild Traumatic Brain Injury

Thysen, J.A. Lee-Wilk, T., Mackenzie, C., Kane, R.L., Spector, J., Auman, K., Kufera, J., Murdock, K., Imle, P., and Dischinger, P.

Objective: To assess the relationship between S100B protein (a biological marker of astroglial cell death representative of CNS damage) and the Word Memory Test (WMT), a test of effort and motivation, in a sample of participants with mild traumatic brain injury (mTBI). The WMT is viewed as a test more sensitive to effort than to brain injury. We hypothesized there would be no relationship between S100B and WMT performance.

Participants and Methods: Thirty-four participants admitted to an ER of an urban hospital, ages 18-64, with Glasgow Coma Scales between 13-15, participated in this longitudinal investigation. S100B protein was measured upon admission, within 3-10 hours post-injury. Each participant was administered the WMT 7-10 days following the injury. Repeat WMT data were also available for 32 participants 3 months post injury.

Results: At 7-10 days, 7 participants (18%) failed the Immediate Recall trial (IR) and two participants (5%) failed the Delayed Recall trial (DR) of the WMT. These same two individuals also failed the IR condition. At 3 months, 1 individual failed IR and none failed DR. Results of regression analyses indicated no relationship between S100B protein levels and performance on WMT performance at both one week and three months.

Conclusion: No relationship was demonstrated between a biological maker of brain injury (S100B) and WMT performance. A 5% failure rate on both IR and DR was observed at one week. No participant failed both IR and DR at 3 months.

APPENDIX

ABSTRACT SUBMISSION
Department of Defense Military Health Research Forum, San Juan Puerto Rico, April 25-28, 2004

SERIAL ASSESSMENT OF MILD HEAD INJURY: EARLY PREDICTORS OF OUTCOME

Dischinger PC, Cooper C, Mackenzie CF, Romani W, Spector J

University of Maryland School of Medicine, Baltimore, MD 21201, USA

BACKGROUND/PURPOSE: The goal of this research endeavor is to identify a cohort of patients with mild TBI (traumatic brain injury) and follow them for a period of one year (1) to determine injury outcomes and (2) to identify those factors that best predict those patients with long-term sequelae. **METHODS:** Identify 300 patients with a mild TBI and obtain baseline measures including biochemical markers, balance measures, clinical findings and neurometric tests. Subjects will be followed at 3-5 days, 7-10 days, 3-, 6-, and 12-months post injury. **RESULTS:** We have only just begun patient recruitment and therefore have no results yet. By April, we should have preliminary findings available. **CONCLUSIONS:** The anticipated result is that biochemical and/or balance measures will add prognostic power to the prediction of long-term outcomes, and thus, could be used in the field to determine the disposition of soldiers who incur mild traumatic brain injury.